PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MBM & CO.
P.O. Box 809
Station B
OTTAWA, Ontario
Canada, K1P 5P9

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 07 June 2005 (07.06.2005)

Applicant's or agent's file reference
683-134PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000040	12 January 2005 (12-01-2005)	12 January 2004 (12-01-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 48/00, A61K 31/7088, A61K 31/7125, A61K 38/19, A61P 35/00

Applicant
GENESENSE TECHNOLOGIES INC. ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	11 May 2005 (11.05.2005)	Debora Fujimoto (819) 997-1855

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of materiai

      [X] on paper

      [X] in electronic form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [X] filed together with the international application in electronic form

      [ ] furnished subsequently to this Authority for the purposes of search.

3 [X] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[ ] claim Nos.

because:

[X] the said international application, or the said claim Nos. 18 to 34 relate to the following subject matter which does not require an international search *(specify)* :

Although claims 18 to 34 encompass a method of treatment of the human/animal body which this Authority is not required to examine under Rule 67.1(iv) of the PCT, the written opinion has been established on the basis of the alleged effects of the compounds referred to therein.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos. are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 1-55	YES
	Claims	NO
Inventive step (IS)	Claims	YES
	Claims 1-55	NO
Industrial applicability (IA)	Claims 1-55 (partially)	YES
	Claims 1-55 (partially)	NO

2. Citations and explanations :

D1 LEE Y et al. GTI-2040, an antisense agent targeting the small subunit component (R2) of human ribonucleotide reductase shows potent antitumor activity against a variety of tumors. CANCER RES 01.06.2003 Vol 63, pages 2802-2811

D2 WO 0047733 A1 (GENESENSE TECHNOLOGIES INC.) 17.08.2000

D3 WO 9800532 A3 (WRIGHT JA & YOUNG AH) 08.01.1998

D4 AGRAWAL S & KANDIMALLA ER. Antisense and/or immunostimulatory oligonucleotide therapeutics. CURR CANCER DRUG TARGETS 2001 Vol 1, pages 197-209

D5 VOSE JM et al. Update on epidemiology and therapeutics for non-Hodgkin's lymphoma. HEMATOLOGY (AM SOC HEMATOL EDUC PROGRAM BOOK, The American Society of Hematology) 2002 pages 241-262.

D6 LEPOIVRE M et al. Alterations of ribonucleotide reductase activity following induction of the nitrite-generating pathway in adenocarcinoma cells. J BIOL CHEM 25.08.1990 Vol 265(24), pages 14143-14149

D7 MADER RM et al. Transcription and activity of 5-fluorouracil converting enzymes in fluoropyrimidine resistance in colon cancer *in vitro*. BIOCHEM PHARMACOL 1997 Vol 54, pages 1233-1242

D1-D3 disclose antisense oligonucleotide sequences (ODNs) to human ribonucleotide reductase R2 which are encompassed by the antisense ODNs of the present application. D1 additionally discloses that of 102 antisense ODNs screened for the ability to inhibit *R2* mRNA and cancer cell proliferation in vitro, 30 candidate ODNs were chosen for analysis *in vivo*. In assays with these 30 candidate ODNs, 18 ODNs were found to result in varying levels of antitumor activity. One antisense ODN, GTI-2040, which has a sequence that is identical to SEQ ID NO:1 of the present application, was selected for further *in vivo* assays and development (page 2804, first column, second paragraph). Thus, several *in vitro* and *in vivo* criteria must be met in order to determine if a particular antisense ODN has potential for treatment of cancer (page 2808, second column, last paragraph).

D2 further discloses at page 52, line 17, that antisense ODNs may be used in conjunction with chemotherapeutic agents or other anti-tumorigenic treatments (page 53, lines 5-7). The phrase "anti-tumorigenic treatment" encompasses an immunotherapeutic agent. D2 specifically discloses that cells treated with an antisense ODN to ribonucleotide reductase R2 had increased sensitivity to one of the three chemotherapeutic drugs, hydroxyurea, *N*-(phosphonacetyl)-L-aspartate (PALA), and methotrexate (MTX) (page 78; Table 7).

D3 further discloses the use of an antisense ODN to inhibit tumor growth (page 5, lines 23-25; page 8, line 35 to page 9, line 13), compositions comprising an antisense ODN having the identical sequence to SEQ ID NO:1 of the present application and a chemotherapeutic agent, and use thereof for the manufacture of a medicament and for the treatment of cancer cells (page 5, lines 6-10).

(Continued in Supplemental Box)

Box No. VII **Certain defects in the international application**

The following defects in the form or contents of the international application have been noted :

The description does not comply with Rule 91 of the PCT. The following typographical errors have been noted:
(a) Table 11, under the heading of "Cell Line: Mouse SC2", in the term "AS-II-326-20" ; and
(b) Table 13, under the heading of the % inhibition of colony forming ability: (1) for AS-II-225-20, under column MDA-MB0231, in the value "4537"; (2) for AS-II-253-14, under column HeLa S3, in the value "9699"; and (3) for AS-II-2083-20*, under column HeLa S3 cells, in the value "696".

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Description Defects:
On page 12, line 29 to page 13, line 1, the US patent documents, US 5,998,383 and US 6,121,000, are incorporated by reference, and thus, do not comply with Article 5 of the PCT. The description shall be complete in and of itself. A person skilled in the art should be able to understand the patent specification without reference to any other document.

Drawing Defects:
The drawings do not comply with Rule 11.11 of the PCT. The drawings shall not contain text matter, except for a single word or words, when absolutely indispensible. The figure legends should be removed and the information incorporated into the description. Further, the titles in Figs. 9-26 should be removed.

Additionally, the drawings do not comply with Rule 11.13 (c) and (h) of the PCT. The height of the numbers and letters shall not be less than 0.32 cm, and the scale of the drawings shall be such that reproduction to a size of two-thirds would enable all details to be distinguished without difficulty. Figure 17 at full scale size, for example, contains lettering that is illegible.

Claim Defects:
Claims 1-55 do not comply with Article 6 of the PCT. Claims directed to the combination product comprising any antisense oligonucleotide (ODN) of between 7 and 100 nucleotides complementary to a mammalian ribonucleotide reductase R2 subunit mRNA, any immunotherapeutic agent, and optionally, any chemotherapeutic agents (claims 1-17), the use thereof for the manufacture of a medicament (claims 35-51), the method for the treatment of any cancer (claims 18-34), and the pharmaceutical kit comprising an antisense ODN and an immunotherapeutic agent (claims 52-55), are not fully supported in the description. The present application discloses only combination products comprising antisense ODN sequences consisting of 20 nucleotides and the specific use of the antisense ODN consisting of 20 nucleotides, depicted in SEQ ID NO:1; no antisense ODN shorter than 20 nucleotides or between 21-100 nucleotides in length is disclosed. D1 and D3 disclose a specific antisense ODN that is identical to that depicted by SEQ ID NO:1 of the present application, for use to treat cancer.

Claims 1, 18, 35, and 52 do not comply with Article 6 of the PCT. The phrases "an antisense oligonucleotide of between 7 and 100 nucleotides in length comprising at least 7 consecutive nucleotides complementary to a mammalian ribonucleotide reductase R2 mRNA" and "one or more immunotherapeutic agents" define the contemplated nucleotide sequence of the antisense ODN and the contemplated immunotherapeutic agent, respectively, in a vague manner, resulting in a lack of clarity.

Claims 7, 9-11, 24, 26-28, 41, 43-45, and 55 do not comply with Article 6 of the PCT. The following terms cause a lack of clarity: "advanced" (claims 7, 24, and 41), "first-line" (claims 9, 26, 43, and 55), "non-specific" (claims 10, 27, and 44), and "specific" (claims 11, 28, and 45).

Claim 20 does not comply with Rule 6.4 (b) of the PCT. Claim 20 refers to the combination product of claim 19, but claim 19 is a method.

Claims 23-34 do not comply with Rule 6.4 (b) of the PCT. Claims 23-34 are partially directed to the method of claim 20, but claim 20 is directed to the combination product.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: **Box V.** (continued)

D4 reviews antisense oligonucleotides targeted to different genes (Table 1) used to treat cancer in clinical trials, including an antisense ODN to ribonucleotide reductase. Cancer combination therapy with an antisense ODN and a chemotherapeutic agent are known (page 198, column 1). Further, the use of an antisense oligonucleotide having CpG dinucleotides that induces a number of cytokines, including IL-12, IL-6, IFN-γ, and TNF-α, as an immunotherapeutic agent for the treatment of cancer is disclosed on pages 202-205. Thus, an antisense ODN may comprise both the antisense and the immunotherapeutic components of the combination product in the present application.

D5 discloses the use of antisense oligonucleotides to Bcl-2, when used in combination with standard anticancer therapy including cytotoxic chemotherapy and immunotherapy, show synergistic enhancement of tumor cell death *in vitro* (page 249). The use of monoclonal antibodies for immunotherapeutic treatment of patients having non-Hodgkin's lymphoma resulted in antilymphoma responses that lasted for several years (page 250, second column to page 251, first column). Therefore, the use of an antisense ODN and an immunotherapeutic agent, or the use of the combination of an antisense ODN, chemotherapeutic agent, and immunotherapeutic agent is disclosed.

D6 discloses that a murine adenocarcinoma cell line was stimulated to generate nitrite when stimulated with γ-interferon (IFN-γ) and tumor necrosis factor (TNF) and/or bacterial lipopolysaccharide (LPS), i.e., immunotherapeutic agents, and that induction of nitrite resulted in inhibition of ribonucleotide reductase enzyme activity.

D7 discloses that use of the combination of an antisense ODN to ribonucleotide reductase R2 (Table 2) and 5-fluorouracil resulted in a synergistic effect and significantly reduced colon cell growth *in vitro*.

Novelty:
The problem to be solved is the provision of a product comprising an antisense oligonucleotide (ODN) to ribonucleotide reductase R2, one or more immunotherapeutic agents, and optionally, one or more chemotherapeutic agents, use thereof for the manufacture of a medicament and for the treatment of cancer, and a pharmaceutical kit comprising said antisense ODN and an immunotherapeutic agent.

D1-D3 disclose the antisense ODN to human ribonucleotide reductase R2 that is encompassed by the antisense ODNs of the present application. D1 and D2 disclose an antisense ODN having a sequence that is identical to SEQ ID NO:1 of the present application. D1 does not disclose the combination product, the use thereof for the manufacture of a medicament and for the treatment of cancer, and the pharmaceutical kit comprising an antisense ODN and an immunotherapeutic agent. D2 does not disclose the combination product, use thereof, method for treatment of cancer, and a pharmaceutical kit comprising the combination product. D3 discloses the combination product comprising an antisense ODN to human ribonucleotide reductase R2, that is encompassed by those of the present application, an immunotherapeutic agent, and the combination product of said antisense ODN and a chemotherapeutic agent. However, D3 does not specifically disclose the antisense ODN having a sequence that is identical to SEQ ID NO:1 of the present application. D4-D7 disclose that the use of antisense ODNs, chemotherapeutic agents and immunotherapeutic agents in various combinations for the treatment of cancer is known. D4-D7 do not specifically disclose the combination an antisense ODN to human ribonucleotide reductase R2 and an immunotherapeutic agent. Thus, in view of any one of D1-D7, the subject matter of claims 1-55 is novel and complies with Article 33(2) of the PCT.

Inventive Step:
D4 or D5 disclose the combinations of (1) an antisense ODN to a specific gene and an immunotherapeutic agent and (2) an antisense ODN to a specific gene and a chemotherapeutic agent for use in treating cancer. D6 specifically discloses that immunotherapeutic agents inhibit ribonucleotide reductase enzyme activity and are used to inhibit cancer cell proliferation. D7 discloses that the combination of antisense ODN to ribonucleotide reductase and a chemotherapeutic agent reduced cancer cell growth *in vitro*. In view of any one of D1-D3, discussed above, taken together with any one of D4-D7, claims directed to the combination product comprising an antisense ODN to ribonucleotide reductase R2, an immunotherapeutic agent, and a

(Continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box V.** (continued)

chemotherapeutic agent (claims 1-17), use thereof for the manufacture of a medicament (claims 35-51) and to treat cancer (claims 18-34), and pharmaceutical kits comprising said antisense ODN and an immunotherapeutic agent (claims 52-55), lack an inventive step. Thus, claims 1-55 do not comply with Article 33(3) of the PCT.

Industrial applicability:
For the assessment of claims 18 to 34 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation. The methods *per se* defined in claims 18-34 relate to subject matter which this Authority is not obliged to examine under Rule 67.1(iv) of the PCT, but the alleged effects of specific compounds referred to therein for the treatment of cancer appear to represent subject matter that has industrial applicability under Article 33(4) of the PCT.

However, the antisense ODN, immunotherapeutic agent, and chemotherapeutic agent comprising a combination product are defined in such a vague and broad manner as to result in combination products which lack industrial applicability. Merely providing a list of antisense oligonucleotides (Table 1), immunotherapeutic agents (pages 25-30), and chemotherapeutic agents (Table 2) is not sufficient to establish the industrial applicability of the combination product comprising a specific antisense ODN, a specific immunotherapeutic agent and a specific chemotherapeutic agent, use thereof for the manufacture of a medicament and to treat cancer, and a pharmaceutical kit comprising a specific antisense ODN and a specific immunotherapeutic agent. Moreover, D1 discloses that based on the *in vitro* assays of 102 antisense ODNs to ribonucleotide reductase R2, which overlap the antisense ODNs of the present application, only 30 candidate ODNs were selected for *in vivo* analysis. The results of said *in vivo* assays, demonstrated that 18 ODNs displayed varying levels of antitumor activity; one antisense ODN, identical to SEQ ID NO:1 of the present application, was further characterized. In view of D1, it is clear that not all of the antisense ODNs claimed in the present application have industrial applicability. Therefore, not all of the combination products, uses and methods thereof, and pharmaceutical kits in the present application will necessarily have industrial applicability. The present application discloses the combination product of an antisense ODN having the sequence depicted in SEQ ID NO:1 and an immunotherapeutic agent selected from interferon-alpha or interleukin-2, to treat renal cancer, which appears to have industrial applicability.

In view of D1, claims 1-55 partially lack industrial applicability under Article 33(4) of the PCT.